

REVIEW

Postmarketing evaluation on the safety and effectiveness of Dengzhanxixin injection made from Dengzhanxixin (*Herba Erigerontis Breviscapi*)

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Supported by National Science and Technology Major Projects for "Major New Drugs Innovation and Development": Study on Key Technologies of Postmarketing Evaluation for Chinese Medicine (No. 2009ZX09502-030)

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Accepted: June 19, 2014

enced renal tubular damage at 480 mg/kg. However, the dose of 120 mg/kg is safe and non-toxic, which is 40 times above the clinical daily maximum. Beagles had increased serum creatinine at 160 mg/kg. In a prospective study, 15 962 cases experienced 16 ADR/ADE. The rate of ADR/ADE was 0.1002%. ADR symptoms included rash (16.00%), chills (16.00%), and fever (16.00%).

CONCLUSION: There is significant evidence that DZI is safe and effective in a clinical setting.

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Key words: Product surveillance, postmarketing; Safety; Treatment outcome; Erigeron; Dengzhanxixin injection

Abstract

OBJECTIVE: To assess the safety and effectiveness of Dengzhanxixin injection (DZI) extracted from Dengzhanxixin (*Herba Erigerontis Breviscapi*) and identify its potential risks.

METHODS: A series of studies were conducted on the production process, quality standards, and pharmacology. Postmarketing clinical studies and literature reviews including adverse reactions (ADR), adverse events (ADE), case analysis and systematic reviews were also conducted. Data from the hospital information system and spontaneous reporting system were analyzed.

RESULTS: The acute toxicity test indicated that the Lethal Dose 50 test (LD₅₀) dosage was 250 times more than the clinical maximum daily dosage (6 mg/kg). In long-term toxicity tests, rats experi-

INTRODUCTION

Dengzhanxixin injection (DZI), manufactured by Yunnan Biovalley Pharmaceutical Co., Ltd., (YBPC) under Approval No. G.Y.Z.Z. Z53021569, is a sterile aqueous injection made from active ingredients like phenolic acids. These compounds are extracted from Dengzhanxixin (*Herba Erigerontis Breviscapi*), which is a medicinal plant grown in Yunnan province. Dengzhanxixin (*Herba Erigerontis Breviscapi*) mainly contains scutellarin (C₂₁H₁₈O₁₂) and various isomers of caffeic acid ester (C₂₅H₂₄O₁₂). DZI can activate blood, remove stasis, dredge meridians, and alleviate pain, and is parenterally administered to treat ischemic stroke and angina pectoris in coronary heart disease (CHD). To assess whether it is safe and effective in clinic, and to identify its potential risk factors, YBPC has carried out a series of studies on DZI. These studies include its production

process, quality standards and pharmacology, postmarketing clinical studies, and postmarketing safety evaluation.

QUALITY CONTROL

The raw material for DZI is the whole plant of Dengzhanxixin (*Herba Erigerontis Breviscapis*). YBPC has established a Good Agricultural Practices (GAP) base in Mile county of Yunnan province as required by China Food and Drug Administration to plant, harvest, process, and store the raw material in accordance with GAP. The suppliers of the raw material have been certified in accordance with GAP, and they are qualified for planting and sales. The solution contains two active ingredients: flavonoids and caffeic acid esters. For the raw material, YBPC not only controlled the content of scutellarin in accordance with the Chinese Pharmacopoeia 2010: Part I, but also developed more stringent indicators for internal control. In addition to the scutellarin content required to meet the relevant requirement, the content of total caffeic acid esters was controlled through Ultraviolet-visible spectroscopy spectrophotometry. The raw material is not used for production of the injection unless the content of the two ingredients is adequate.¹

In the production process of DZI, the important steps are the extraction of raw material and solution preparation. Therefore, YBPC detailed the column technology so that toxic pyromeconic acid was fully eluted to retain the active ingredients. A total of eight control points were set for extraction, separation, and purification. Online or offline analyses of chemical and physical indicators for these eight control points are conducted. High-performance liquid chromatography (HPLC) and fingerprints are analyzed during the extraction-separation process to control ingredient content and yield. During solution preparation, a refined preparation is conducted with respect to the nature of the caffeic acid esters. The sterile process involves incomplete sterilization, sterilizing filtration, and nitrogen protection to ensure that the products are sterile.

Non-clinical safety and pharmacological study

In October 1999, YBPC entrusted Tianjin Institute of Pharmaceutical Research (Tianjin, China) to conduct a non-clinical safety and pharmacological study on the acute, long-term, and special toxicology of DZI, as well as a general pharmacological study. The results are as follows:

Acute toxicity test: the acute toxicity test indicated that mice had reduced activity, inactivity, polypnea, and lip and tail cyanosis, followed by behavioral disorder, convulsions, startling and eventual death after receiving DZI through single doses of intravenous (IV) or intraperitoneal (IP) injection. The female and male Lethal Dose 50 test (LD₅₀) for IV DZI was 1676.75 and

1740.76 mg/kg, respectively, with no significant difference between sexes. The IP LD₅₀ of DZI was 1770.92 mg/kg, which was equivalent to more than 250 times the maximum daily dosage (6 mg/kg) used in clinical applications.

Long-term toxicity test: for long-term toxicity tests, rats were administered 30, 120, and 480 mg/kg of DZI through IP injection once a day for 2 months. General drug reactions were observed, and hematological, blood biochemical, and histopathology indexes were examined. A slow increase in body weight was observed in the male rats in the 480 mg/kg dose group. Pathological examination revealed mild opacity and swelling in the renal tube epithelium of cortex in renal tissue. No obvious changes or damage associated with the drug were found in the 120 and 30 mg/kg dose groups, and no delayed toxicity was found during the 2-week recovery after withdrawal of the drug. This indicates that the 120 mg/kg dose of DZI was not toxic for rats. This dosage is equivalent to more than 40 times the maximum daily dose (6 mg/kg) used in clinical applications.

The results of the long-term toxicity test on Beagle dogs showed that the adverse reactions of the animals in the 160 mg/kg dose group during the 60-day continuous venous infusion of DZI included obvious drooling, extended tongue, nausea, and vomiting. Symptoms after administration included immediate loss of appetite, procumbent stance, reduced activity, and slower breathing and heart rate. Blood biochemical examination revealed increases in the level of creatinine on the 30th day of administration. During administration, adverse reactions such as drooling, extended tongue, nausea, and vomiting were found in some animals in the 40 mg/kg dose group, and there was only one animal with a reaction equivalent to that of animals in the 160 mg/kg dose group. Animals receiving the drug remained procumbent and lethargic after administration, and the blood biochemical examination revealed increases in total protein after administration. No significant influences on animals' spirits, behavior, diet, excrement, body weight, and urine biochemical indicators were seen in the 10 mg/kg dose group. Compared with the control group, no significant changes were found in hematological examination, blood biochemical examination, ophthalmologic examination, electrocardiography, and bone marrow examination in the 10 mg/kg group. Therefore, 10 mg/kg was the level at which no adverse effects were observed.

Special toxicology tests: DZI was injected IV into rabbits *via* ear veins once a day for 3 days. No obvious irritation effect was observed at the injection sites. Hemolysis tests showed no hemolysis. DZI was injected IP into guinea pigs once every other day, three times. No positive allergic reactions were found after intravenous injection of the drug on the 14th and 21st day after first administration.

General pharmacologic study: a dose of 4 mg/kg DZI was IV injected into rats. Compared with the control group, behavior disorder from cerebral ischemia caused by ferric chloride was significantly improved by reducing the infarct area. Cerebral blood flow of rats suffering from microcirculatory disturbance from high-molecular dextran was significantly improved by reducing blood viscosity of model rats. Further, the thrombus formation time of normal rats was remarkably delayed and platelet aggregation rate was reduced after administration of IV DZI.

Treatment of ischemia and hemodynamics: a dose of 4 mg/kg DZI was injected IV into Beagle dogs. Compared with the control group, the degree of acute ischemia in dogs with a ligated left anterior descending artery was significantly improved. Therefore, DZI can reduce the myocardial infarction area. The results of cardiac hemodynamic tests on anaesthetized open-chest dogs indicated that a certain dose of DZI could reduce blood pressure, left ventricle pressure (LVP), maximum LVP rate, left ventricle work, and coronary resistance, while having no remarkable influence on heart rate, left ventricular end-diastolic pressure, total peripheral resistance, cardiac function, and other hemodynamic parameters. Therefore, DZI has an anti-myocardial ischemia effect by relieving cardiac after-load, expanding the coronary arteries and peripheral vasculature, and reducing returned blood volume and cardiac work.²

Postmarketing clinical study

A multi-center randomized controlled trial of DZI in the treatment of acute ischemic stroke: from June 2008 to June 2010, relying on Study on Traditional Chinese Medicine Schemes for Early Recovery from and Recurrence Prevention of Ischemic Strokes (No. 2007AA02Z4B2), an 863 Program of the Ministry of Science and Technology led by Wang Yongyan and researcher Xie Yanming from the Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, YBPC conducted a multi-center randomized controlled clinical study on the treatment of acute ischemic strokes with DZI. This study involved 13 centers nationwide, in which a central randomized system for clinical study was applied. Patients were randomized into a DZI (Dengzhan group) and Western medicine group (WM group). There were 343 cases in the Dengzhan group and 335 cases in the WM group. The Dengzhan group included DZI with basic therapy with Western internal medicine and the recovery techniques of Traditional Chinese Medicine (TCM). Clinical safety evaluation mainly involved observing laboratory examination indicators, adverse events, and their incidences. In the Dengzhan group, 11 adverse drug reactions/events (ADR/ADE) occurred, of which four cases were associated with DZI based on a causal relationship, with the incidence of ADRs being 1.17% (4/343). The symptoms of ADRs included fever, chills, rash, nausea, dizziness, and palpi-

tations, and no serious ADRs occurred.³

Registry-based postmarketing clinical safety monitoring study: the project "Registry-based postmarketing clinical safety monitoring study of DZI" comes from the Study on Key Technologies of Postmarketing Evaluation of Chinese Medicine (No. 2009ZX09502-030), a national science and technology major project "Major New Drug Development" presided over by Yanming Xie, researcher from the Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences. A total of 30 000 cases are expected to enroll in this study. In March 2012, the study was approved by the ethics review board of the institute (Approval No. 9-1) and the protocol registration was completed at ClinicalTrials.gov (ID: NCT01612585). Monitoring has been initiated in 42 sub-centers of six hospitals: Jiangsu Provincial TCM Hospital, Guangdong Provincial TCM Hospital, the First Affiliated Hospital of Henan University of TCM, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, General Hospital of Tianjin Medical University, and General Hospital of Ningxia Medical University. Level-3 quality control was practiced in the project. From May to June 2013, three of the lead hospitals (the Second Affiliated Hospital of Guangzhou TCM University, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, and Jiangsu TCM Hospital) received the first round of level-3 auditing. The audit experts carefully checked the qualifications of the monitored hospitals, research staff, monitoring tables, and original information and data to locate problems and summarize on-site audit opinions on the monitored hospitals. By November 2013, 15 962 cases were enrolled in monitoring, with 16 ADR/ADE cases being reported. The ADR rate was 0.1002%. ADR symptoms included: rash (eight cases/50%), chills (two cases/12.5%), fever (one case/6.25%), shortness of breath (one case/6.25%), palpitation (one case/6.25%), headache (one case/6.25%), lower extremity edema (one case/6.25%), elevated blood pressure (one case/6.25%), and abdominal pain (one case/6.25%).

Spontaneous reporting system (SRS) data analysis: data mining analysis and early warning signals detection were conducted with the proportional reporting ratio (PRR) and Bayesian confidence propagation neural network methods (BCPNN) using ADR reports on DZI in the SRS database of the State Adverse Drug Reaction Monitoring Center.⁴ The results showed that, among the 1390 ADR reports, there were 71 reports on serious ADRs, accounting for 5.11%. The frequency of ADRs for men was higher than that for women. Most serious ADRs occurred in elderly patients aged 60 and over (64.03%). The top 10 ADR symptoms included pruritus, rash, dizziness, chills, palpitation, headache, fever, suffocation, nausea, and flush. The most common systems and organs involved in ADR were "damage to skin and its accessory organs" (551 in-

stances). After confounding factors were controlled for with the propensity score, the PRR and BCPNN methods both showed that headache, dizziness, palpitation, and chills were early warning signals of adverse reactions to DZI. These ADR symptoms were found in the specifications of DZI, while suffocation, nausea, allergies, and vomiting, which clinically occurred at a high frequency, were not found in the drug instructions. Although no early warning signals were well defined, particular attention should be paid to these symptoms during clinical use.

Hospital information system (HIS) data analysis

Data from the HIS of 20 hospitals across China were used to conduct clinical safety and effectiveness analysis of DZI.

Total population descriptive analysis: of the 21 498 patients, those aged 45-80 accounted for 78%, and there were more male patients than female patients. In most patients, the dose was 30-40 mL each time, and the treatment cycle was 8-12 days, which basically falls within the range specified in the manufacturer's directions for DZI. DZI was given to 95.51% of patients within 3 days after hospitalization. Common concomitant medications were atorvastatin, probucol, and aspirin for cerebral infarction, and metoprolol, aspirin, and isosorbide dinitrate for coronary heart disease.⁵

Outcome analysis of DZI in the treatment of cerebral infarction: a total of 2512 cases of cerebral infarction were divided into an observation (given DZI) and control group (1008 and 1504, respectively), with mortality as the outcome. Using generalized boosted models (GBM) to score weighted regression on age, gender, and a database of 72 variables to be balanced, there were significant differences in the observed group and the control group ($P < 0.001$), suggesting that DZI may reduce the death rate in patients with cerebral infarction.⁶

The influence of Erigeron injection on coronary heart disease outcomes: a total of 2325 cases of coronary heart disease were divided into an observation (given DZI) and control group (768 and 1557, respectively). Using GBM to score weighted regression on age, gender, and a database of 72 variables to be balanced, three kinds of logistic regression analyses were applied to find the cure rate and mortality of coronary heart disease. After controlling for confounders, there was a significant difference in the cure rate and mortality rate between the two groups, which indicated that the combined use of DZI might improve the cure rate, and reduce the mortality of patients with coronary heart disease.^{7,8}

Literature review: cross search was used to search the Chinese Biomedical Literature Service System (SinoMed), Wanfang Database, China National Knowledge Infrastructure Database and China Science & Technology Journal Database (from inception to March 15, 2012). A total of 732 articles about DZI were retrieved.

ADR case analysis: thirty articles concerned the safety of DZI. After eliminating three duplicate articles, 11 articles concerning drug incompatibility, and one article involving clinical safety cases, there were 15 articles reporting individual cases, in which 25 cases were involved. The 25 case reports involved 18 serious ADR cases with no deaths. The ADRs included 10 cases of anaphylactic shock, two cases of acute kidney failure, four cases of abnormal liver function, one case of auricular premature beat, and one case of bronchial asthma. Of these 25 cases, the latest ADR occurred 10 days after continuous infusion, and the earliest ADR occurred 3 min after infusion began. The review found that the common symptoms of adverse reactions to DZI as reported in the literature were fever, chills, rash, nausea, palpitation, and dizziness.⁹

Systematic reviews: a total of 17 randomized controlled trials were incorporated into a meta-analysis on treating unstable angina with DZI. The treatment effects on unstable angina in two groups were reported in 16 studies. The DZI treatment group included 765 patients and the control group included 727 patients. The heterogeneity test resulted in $P = 0.11$ and $I^2 = 32\%$. A fixed effect model was used to carry out the Meta-analysis. The treatment effects in the treatment group were better than those in the control group, and the difference was statistically significant ($P < 0.0001$). Fifteen studies reported treatment effects in terms of electrocardiograms for the two groups. The DZI treatment group included 784 patients and the control group included 740 patients. The heterogeneity test resulted in $P = 0.15$ and $I^2 = 28\%$. Fixed effect model analysis was used, revealing that the treatment effects in the treatment group were better than those in the control group in terms of electrocardiograms. The difference was statistically significant ($P < 0.0001$). Therefore, the treatment of unstable angina by combining DZI with ordinary therapy was better than that of treatment with ordinary therapy alone. However, considering the differing quality among studies and possible difficulty in publishing papers reporting negative results, publication bias is possible in the results of the study.¹⁰

CONCLUSION

Since the involvement of DZI in the project "Registry-based Clinical Safety Monitoring Study of Parenterally Administered Chinese Medicine," the following have been published: a literature review report, one systematic evaluation report, one HIS statistical analysis report, one ADR analysis report, and one audit report on DZI. There have also been 10 academic papers published related to the injection. This study summarizes the significant evidence for the safety and effectiveness of the injection in clinical practice.

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